ANESTHESIA AND ANALGESIA

6.1 GUIDELINES and REGULATIONS:

Guidance on the use of anesthetics, analgesics, and other categories of drugs for the prevention or relief of pain and distress in laboratory animals comes from several documents. Appropriate parts of those documents are listed below for your information.

The U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training states the following. " Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative. Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals." Additionally, "Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia. Surgical or other painful procedures should not be performed on unanesthetized animals paralyzed by chemical agents."

The Guide for the Care and Use of Laboratory Animals, states the following: "An integral component of veterinary medical care is prevention or alleviation of pain associated with procedural and surgical protocols. Pain is a complex experience that typically results from stimuli that damage tissue or have the potential to damage tissue. The ability to experience and respond to pain is widespread in the animal kingdom. A painful stimulus prompts withdrawal and evasive action. Pain is a stressor and, if not relieved, can lead to unacceptable levels of stress and distress in animals. The proper use of anesthetics and analgesics in research animals is an ethical and scientific imperative."

The Animal Welfare Act (Public Law 89-544), as amended, requires that institutional veterinarians provide guidelines regarding the use of tranquilizers, anesthetics, analgesics, and euthanasia agents as follows:

1) In the case of a research facility, the program of adequate veterinary care shall include the appropriate use of anesthetic, analgesic, or tranquilizing drugs, when such would be proper in the opinion of the attending veterinarian at the research facility.

The use of these three classes of drugs shall be in accordance with the currently accepted veterinary medical practice as cited in appropriate professional journals or reference guides which shall produce in the individual subject animal a high level of tranquilization, anesthesia, or analgesia consistent with the protocol or design of the experiment.

2) It shall be incumbent upon each research facility through its Animal Care Committee and/or attending veterinarian to provide guidelines and consultation to research personnel with respect to the type and amount of tranquilizers, anesthetics, or analgesics recommended for each species of animal used by that institution.

3) The use of those three classes of drugs shall effectively minimize the pain and discomfort of the animals while under experimentation.

6.2 Functions of the Attending Veterinarian in the Management of Anesthesia and Analgesia:

Provides professional advice on the type of agents that are appropriate for use and establishes dose ranges for each.

Counsels the investigator on appropriate physical facilities and equipment to properly administer general anesthetics and recommends ways to monitor the physical condition of an animal while it is under treatment.

Provides professional expertise in response to medical emergencies if they occur.

Monitors surgical procedures to assess the degree of pain relief required and prescribes appropriate pain relieving drugs.

6.3 Factors Affecting Choice of Anesthetic and Analgesic Regimens:

Dosage charts for anesthetic and analgesic agents usually state an amount that would be expected to produce a desired level of effectiveness under average conditions. These charts must be used with this principle in mind.

Another principle to remember when selecting an anesthetic or analgesic agent for use on a protocol is that there are many factors that can affect the activity of anesthetics and analgesics so they must be considered for their potential effects on dosage.

The species, strain, sex, age, physiologic status, relative body size, disposition/demeanor, presence of concurrent pain or distress, concurrent medication or other treatments are known to either increase or decrease the amount of a drug that is needed to produce a desired effect in an individual animal.

The duration of anesthesia produced by the agent should coincide with the expected duration of the procedure and the duration of analgesia produced by the analgesic should coincide with the duration of the pain generated by the procedure. The depth of the anesthesia or analgesia provided is dependent on the pain potential of the procedure.

The time needed for postsurgical recovery from anesthesia and the frequency of administration of analgesics should coincide with the level and frequency of postsurgical monitoring that is available. When personnel and resources for proper postsurgical monitoring of patients are limited, an anesthetic that has a short recovery time and an analgesic that has a long duration of activity should be selected.

Special facilities and equipment are required for the administration of volatile anesthetics and for scavenging excess gas to protect the operator. If these facilities and equipment are not available an injectable anesthetic is the best choice.

Softwood bedding (eg cedar , pine) can change the nature of liver enzymes with a concurrent change in the manner by which anesthetics are metabolized. For this and other reasons, some other form of bedding should be used with rodents.

Personal knowledge, experience, preference, and skill with available agents and equipment can affect the outcome of the use of anesthetics and analgesics. These factors must be taken into consideration when selecting the drugs to be used.

6.4 Safety Precautions:

It is necessary to protect humans from vapors of volatile anesthetics by using gas scavenging systems. Monitor the use of chemical agents and assure that product safety recommendations are followed to protect the health and welfare of the humans and animals that are exposed to the agents.

Many of the drugs described herein have the potential for human abuse so they must be stored in a manner that minimizes that risk. Drugs that come under the control of the Drug Enforcement Agency (DEA) must be stored in a double-locked cabinet in a secure area (see 6.5 below for more detail).

6.5 Controlled Substances:

NIH Policy Manual 1345, HANDLING AND SAFEGUARDING OF CONTROLLED SUBSTANCES FOR NONHUMAN USE describes policies and procedures for handling and safeguarding controlled substances for nonhuman use (i.e., those to be administered to animals or used for in vitro research) at the National Institutes of Health (NIH) Intramural Research Program, from acquisition through disposal, as required by the Comprehensive Drug Abuse Prevention and Control Act of 1970, as amended. A copy of the manual chapter can be found at: http://oacu.od.nih.gov/NIHpolicy/1345.pdf.

The ORS/DIRS/VRP (VRP)Pharmacy is the only organization authorized to acquire Controlled Substances and DEA Regulated Chemicals for nonhuman use at the NIH. All controlled substances, including vendor samples and those supplied by other ICs must be procured through the VRP Pharmacy.

The NIEHS in Research Triangle Park, NC, NIA/IRP and NIDA/IRP in Baltimore, MD, NIAID/RML in Hamilton, MT, NIDDK in Phoenix, AZ, and NCI/FCRDC in Frederick, MD, are authorized to procure controlled substances and DEA regulated chemicals for nonhuman use under research licenses granted to those organizations by the DEA.

Public Law 91-513, Section 202:

"There are five schedules of controlled substances, to be known as schedules I, II, III, IV, and V. Such schedules shall initially consist of the substances listed in this section.

The schedules established by this section shall be updated and republished on a semiannual basis during the two-year period beginning one year after the date of this title and shall be updated and republished on an annual basis thereafter."

Oversight for compliance with the law resides with the Drug Enforcement Agency (DEA).

Placement on Schedules, Findings Required:

"Except where control is required by United States obligations under an international treaty, convention, or protocol, in effect on the effective date of this part, and except in the case of an immediate precursor, a drug or other substance may not be placed in any schedule unless the findings required for such schedule are made with respect to such drug or other substance. The findings required for each of the schedules are as follows:

Schedule I.

The drug or other substance has a high potential for abuse.

The drug or other substance has no currently accepted medical use in treatment in the United States.

There is a lack or accepted safety for use of the drug or other substance under medical supervision.

Schedule II.

The drug or other substance has a high potential for abuse.

The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.

Abuse of the drug or other substances may lead to severe psychological or physical dependence.

Schedule III.

The drug or other substance has a potential for abuse less than the drug or other substance in schedules I and II.

The drug or other substance has a currently accepted medical use in treatment in the United States.

Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.

Schedule IV.

The drug or other substance has a low potential for abuse relative to the drugs or other substances in schedule III.

The drug or other substance has a currently accepted medical use in treatment in the United States.

Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drug or other substance in schedule III.

Schedule V.

The drug or other substance has a low potential for abuse relative to the drug or other substance in schedule IV.

The drug or other substance has a currently accepted medical use in treatment in the United States.

Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drug or other substance in schedule IV."

6.6 Record Keeping Requirements:

A written record is required when drugs that come under the control of the DEA are used. The record must reflect the purchase/acquisition date of each drug, the volume received, the date and volume of each use of the drug, and the volume of drug remaining in the inventory. Each entry in the record must be signed by the person who is authorized to dispense the drug.

An inventory list of anesthetics, analgesics, tranquilizers, sedatives, and other drugs should be kept.

Individual clinical records should be annotated to reflect the use of the agents described above, showing the date, dose, and any abnormal reactions that occurred.

All records should be stored in such a way that they are readily available for review by members of the institutional animal care and use committee and by other authorized individuals.

6.7 Pretreatment of the Surgical Patient:

Drugs such as anticholinergics, tranquilizers, or sedatives can be given as pretreatment prior to the administration of anesthetics for a variety of reasons. The primary goal in every case is to minimize depression of the central nervous system while assuring that the animal is unconscious and does not feel pain that accompanies the procedure.

Anticholinergics (i.e. atropine sulfate, glycopyrrolate)

These agents block parasympathetic impulses to the cardiopulmonary system, glands and smooth muscle. Consequently, they prevent vaso-vagal reflexes with concurrent slowing of the heart and they reduce salivary gland and bronchial secretions.

Tranquilizers: (eg acetylpromazine)

They may be used to calm the animal by reducing fear and apprehension which facilitates restraint without marked sedation. These animals can be readily aroused by painful stimulation because tranquilizers do not produce analgesia.

Reduce the amount of anesthetic required for induction and maintenance of general anesthesia which decreases the undesirable side-effects of the anesthetic agent.
Reduce involuntary reflex responses that may occur unless deep levels of anesthesia are maintained throughout a surgical procedure.

Provide greater skeletal muscle relaxation when the chemical nature of the anesthetic does not produce enough. This effect is seen in rabbits and cats with the administration of a combination of acetyl promazine and ketamine hydrochloride. This activity is not uniformly as strong, however, as the skeletal muscle relaxation that results from the administration of neuromuscular blocking agents like succinyl choline.

Sedatives: (eg xylazine)

They may be used to depress the CNS and produce drowsiness which also serves to reduce the amount of anesthetic agent that is needed for induction and maintenance of general anesthesia. There is wide species variation in the reaction to these drugs.

Some sedatives, such as xylazine, have analgesic properties which serve to increase the level of analgesia that can be produced through the use of combinations of drugs.

Nonchemical Pretreatment:

Nonchemical pretreatment procedures such as withholding drinking water and food prior to surgery are advisable to prevent regurgitation of stomach contents and subsequent inspiration into the respiratory tract while the animal is anesthetized.

Water can be given ad libitum up to the time of surgery with some species but it should be withheld for several hours for some species particularly ruminants.

Withhold food for: Dogs and cats 8-12 hours; Primates 8-12 hours; Ruminants: 24 hours.

6.8 Tranquilizers and Sedatives:

Definition:

The distinction between tranquilizers and sedatives is mainly semantic. One differentiating characteristic, however, is that tranquilizers at high dose levels tend to produce side effects without a loss of consciousness whereas sedatives at high dose levels cause a profound CNS depression similar to anesthesia.

Functional Uses:

Used primarily for chemical restraint or as preanesthetic medication.

Tranquilizers produce a state of behavioral change in which the animal is relaxed and unconcerned by its surroundings. The animal is often indifferent to minor painful stimuli but will react to higher levels of pain and that reaction may be violent.

Sedatives produce a mild degree of central nervous system (CNS) depression in which the animal is conscious but calm. These agents will produce a psychological calming of an animal but do not exert hypnotic or analgesic effects. Animals can become aroused by the stimulation of painful procedures.

Characteristics:

With the exception of the alpha-2 agonists (e.g., xylazine), these compounds have no significant analgesic activity.

Increased stimulation by loud noises usually reverses the calming effects of these drugs.

When used as preanesthetics, ample time should be allowed for the drug to reach its maximum effect before anesthesia is induced.

Recovery from general anesthesia is generally smoother when these drugs are used as pretreatments.

All tranquilizers and sedatives share the characteristics listed above, but each drug or group of drugs has its own diverse pharmacologic properties and contraindications.

Classifications of Tranquilizers (ataratics or neuroleptics):

Phenothiazine derivatives (e.g., acetylpromazine)

Butyrophenones (e.g., azaperone, droperidol)

Rauwolfia alkaloids (e.g., reserpine, metoserpate hydrochloride)

Benzodiazepines (e.g., diazepam)

Classifications of Sedatives (hypnotics):

Barbiturates (e.g., phenobarbital)

Benzodiazepines (e.g., zolazepam)

Chloral derivatives (e.g., chloral hydrate)

Thiazine derivatives (e.g., xylazines)

Tranquilizer and Sedative Effects:

Phenothiazines:

Make animals more tractable; cause hypotension secondary to peripheral vasodilation; minimally reduce respiratory rate; may lower seizure threshold; cause CNS effects by depressing the brainstem and connections to the cerebral cortex; are metabolized in the liver. NOTE: These agents augment hypothermia through their hypotensive effects so they should be used with caution in small or very old animals.

Acetylpromazine maleate:

Has antiemetic, hypotensive, and hypothermic properties; it is often used in combination with ketamine hydrochloride to increases muscle relaxation; it has been observed to precipitate seizures in gerbils.

Chlorpromazine hydrochloride:

Potentiates barbiturate anesthetics; IM injections in rabbits have been associated with severe myositis at the site of injection ; produces teratogenic effects in rats and mice.

Butyrophenones (droperidal, lenperone, zolazepam):

Cause animals to react indifferently to their surroundings and decreases their motor activity; can cause hypotension,but less than the phenothiazines, and they slightly increase the respiratory rate. Effects of the group are similar to the phenothiazines but they are more potent.
They are used in combination with narcotics to produce neuroleptanalgesic combinations.

Rauwolfia Alkaloids (reserpine and metoserpate):

None of these drugs are commonly used in veterinary medicine.

Benzodiazepines (diazepam, midazolam):

Cause CNS depression; have mild cardiovascular depressant effects at low doses; have little effect on respiration. Effects may vary significantly by species in that they cause minimal sedation in most animals but cause marked sedation in rabbits and rodents.

Since they cause minimal cardiopulmonary depression, they are excellent for old animals and those that are metabolically compromised for some other reason.

Benzodiazepines bind to most plastics; therefore, do not store in plastic syringes.

> Diazepam (Valium®) - Schedule IV drug with anticonvulsant properties; acts on thalamus and hypothalamus with no peripheral blocking actions; metabolized in liver. Good skeletal muscle relaxation.
>
> Diazepam does not mix efficiently with most other drugs in the same syringe but it mixes efficiently with ketamine hydrochloride.
>
> Midazolam (Versed) is a water soluble benzadiazepine.

Alpha-2-adrenergic agonists (e.g., xylazine):

Produce dose-related CNS depression; cause bradycardia, decreased cardiac output, and increased central venous pressure.

Potent sedatives and hypnotics. Good analgesic action.Potentiates most anesthetic drugs.

Cardiovascular and respiratory depression.

Cardiac arrhythmia possible (2nd degree heart block).

Severe respiratory depression when administered with barbiturates or alphaxalone/alphadolone.

Rapid metabolism in swine. Crosses placenta and may cause vomiting.

Barbiturates (e.g., sodium pentothal):

High doses produce general anesthesia but suboptimally low doses will cause an excitement stage. This stage can, and must be, reversed by the administration of an additional volume of anesthetic.

Sodium pentothal and sodium thiamylal, ultrashort acting barbiturates, can be used at lower doses as a sedative and premedication before anesthesia but the dose must be carefully controlled to avoid the excitement stage.

Chloral derivatives (e.g., chloral hydrate):

Chloral hydrate is a reliable sedative hypnotic, however dosages sufficient to provide surgical anesthesia and analgesia approach lethality. Adverse effects include severe respiratory cardiovascular and thermo-regulatory depression. A 5% concentration given IP in rats with proper patient support can provide 2 hours of anesthesia.

Reversal of tranquilizing and sedative effects:

Yohimbine can be used to reverse xylazine. Atipamezole antoagonizes alpha-2 agonists such as xylazine and medetomidine. Flumazenil is the antagonist for benzodiazepines. These reversal drugs are useful in reducing the post-procedural recovery time

6.9 General Anesthetics:

Definition: Substances that produce, in a controllable manner, both loss of consciousness and an absence of motor response to noxious stimuli.

Functional Use: To produce unconsciousness, analgesia, and muscle relaxation sufficient to perform procedures that would otherwise be painful.

General Considerations:

Whenever possible, try a new anesthetic regimen in a limited number of animals before depending on it for surgical or other painful procedures in the research protocol.

Administer anesthetics only to healthy animals or when emergency procedures require their use.

Use these drugs judiciously to minimize the CNS depression necessary for performing the procedure, compatible with the animal's welfare.

Consider to what extent the anesthetic protocol will affect the validity of experimental results and how it will interact with other drugs being used.

Even in the absence of sophisticated equipment, try to have some basic items available to insure adequate ventilation of the animal.

Maintain a patent airway. This is essential if difficulty arises and the subject is to survive. With small animals that are obligate nose breathers (rats, mice, hamsters, guinea

pigs, rabbits), a patent airway is easily maintained if nostrils are not blocked. Other species may require tracheal intubation.

Monitor and maintain body temperature to avoid hypothermia. Conservation of body heat is an integral part of anesthetic management. Core body temperature can fall precipitously during the course of prolonged general anesthesia, especially in small animals. Hypothermia added to other factors can produce an irreversible sequence of events leading to death. Thermostatically controlled heating pads should be used during animal surgery.

Administer warm, balanced electrolyte solutions by continuous I.V. drip throughout the surgical procedure whenever possible to help maintain normal hemodynamics.

The anesthetist's responsibility for the welfare of the animal extends beyond the end of the surgical procedure to the time that the animal is able to maintain itself in sternal recumbency and breathing normally.

Consider the safety of personnel who will be in the area during the use of an anesthetic gases and provide a gas scavenging system.

Dosage principles for general anesthesia:

Evaluate the physical condition of the animal to assure that there is no disease condition that may compromise the health of the animal during anesthesia.

Calculate dose by body weight and age.

Administer drugs to effect. Because of the wide variation within and among species, there is really no such thing as a predetermined anesthetic dose of a drug. General anesthesia must be given "to effect," as measured by physiologic parameters and response to stimuli. It is important to realize that some drugs take time to take effect. Most anesthetic deaths can be attributed to not giving the anesthetic time to work. This is especially true of parenterally administered drugs (e.g., barbiturates) - once they are injected,what the anesthetist can do to control the outcome is limited.

Allow for variations in response to agents between species and between individuals of the same species because the absorption and biotransformation processes can be very different.

Pretreat with tranquilizers or sedatives to decrease the amount of anesthetic needed to prevent pain and distress.

Stages of general anesthesia

Stage I

Stage of analgesia or voluntary movement.

Duration: From onset of administration to loss of consciousness.

Stage II

Stage of delirium or involuntary movement.

Duration: From loss of consciousness to onset of regular pattern of breathing.

Stage III

Stage of surgical anesthesia.

Characterized by unconsciousness, with depression of reflexes; muscular relaxation; slow, regular respiration; and loss of vomiting and swallowing reflexes.

Divided into planes 1 through 4, where plane 1 is light anesthesia, planes 2 and 3 are medium anesthesia, and plane 4 is deep anesthesia.

Stage IV

Characterized by extreme CNS depression.

Death ensues quickly unless resuscitative steps are taken.

Evaluation of effects

Ocular reflexes are quite variable and should not be used as the sole criteria for the evaluation of the adequacy of anesthesia. In general, palpebral reflex associated with touching the eyelids is lost in light to medium planes of surgical anesthesia. Corneal reflexes are very inconsistent between species and should only be used with care. The corneal reflex is lost in the rabbit at very deep planes of surgical anesthesia.

The pedal and palpebral reflexes are absent and the tone of jaw and anal sphincter muscles are relaxed during anesthesia. Rabbits, hamsters and guinea pigs may demonstrate spontaneous movements at all stages and planes of anesthesia. Surgical anesthesia in these species is normally accompanied by the disappearance of head shaking in response to pinching of the ear. Slow regular deep breaths have been demonstrated to be a better sign of the level of surgical anesthesia in rabbits

Monitor depth and rate of respiration (increase in depth and decrease in rate signifies anesthesia). Guinea pigs and rabbits may hold their breath when excited or when exposed to certain inhalational agents. Surgical anesthesia is accompanied by breathing at a slower and more regular rate. Violent alterations secondary to surgical stimulation usually indicate inadequate anesthesia. If the animal is too deep, the inspiratory effort is often labored and coupled with pronounced movement of the abdominal muscles without movement of the thoracic muscles. Because the airways of many laboratory animals are easy to obstruct, the animals neck should be extended during surgical manipulation.

Monitor heart rate (slowing indicates anesthesia) An increase in rate during the performance of a surgical procedure often indicates that the depth of anesthesia is not adequate and the animal is feeling pain.
Monitor body temperature (temperature falls in anesthesia; warming causes faster metabolism of anesthetic) Maintain temperature at normal levels.

Indications of anesthetic overdose:

Heart rate may be rapid or slow depending on the animal's state of physiological decompensation.

Pulse may be weak to imperceptible.

Blood pressure is reduced to shock level.

Cardiac dysrhythmias may occur.

Capillary refill time progressively slows to 3 or more seconds.

Respiration is slow, irregular, and becomes diaphragmatic or may cease.

Mucous membrane and skin colors are pale to cyanotic.

Gastrointestinal, ocular, and musculoskeletal reflexes are greatly diminished or cease.

Intervention for anesthetic overdose:

Mechanically ventilate with oxygen or at a minimum room air. At times respiration can be stimulated digitally by applying mild pressure to the chest wall. If total respiratory collapse is observed, a tight fitting face mask or rubber tube placed over the animals mouth and nose can be used to ventilate the animal. Care must be used to maintain filling pressures below 25-30 cm H2O.

Administer isotonic fluids intravenously or intraperitoneally.

Warm animal to increase body temperature.

Administer antidote, if one exists.

General Anesthetic Agents:

Injectable (Barbiturates):

Once these agents are administered their effects cannot be reversed because the drug must be metabolized or the effects counteracted by the action of another drug.

Many injectable anesthetic agents are controlled substances, i.e. barbiturates, and must be handled in adherence to the Controlled Substances Act.

Many of these agents will produce sedation followed by severe depression and general anesthesia as greater doses are administered. At high doses these agents are often utilized for euthanasia.

Prolonged recovery results from glucose, epinephrine, and chloramphenicol administration, and from hypothermia. Softwood bedding induces hepatic microsomal enzymes in rodents, reducing barbiturate sleeping time.

Some barbiturates are caustic substances when injected into living tissue. Care must be taken to completely avoid subcutaneous or intramuscular injections with these drugs. Intravenous injections are required. Intraperitoneal injections are acceptable only with Pentobarbital Sodium (Nembutal®).

All barbiturates are poor analgesics unless administered to unconsciousness.

Examples:

Pentobarbital sodium (Nembutal®) - short acting; small safety margin, intravenous or intraperitoneal injection.

Thiamylal sodium (Surital®) or Sodium Pentothal - ultra-short acting (15 to 30 minutes). Intravenous injection only. Avoid repeated doses due to cumulative effects. Calculate dose on lean body weight only.

Inhalation Agents

The duration of effect of these agents can be terminated quickly because expiration of the anesthetic gas begins immediately upon termination of the administration of the agent. Inhalant anesthetics have a rapid onset and high degree of controllability.

The reversal process can be hastened significantly by the administration of oxygen after the anesthetic gas is stopped.

Examples:

Halothane (Fluothane®) - highly volatile but relatively insoluble (halothane saturated atmosphere can reach a 30% concentration); requires use of vaporizer for precise concentrations; potent cardiovascular depressant; gives fair muscle relaxation and analgesia; nonexplosive.

Isoflurane - Isomer of enflurane. Maintains cardiac output better than other volatile agents. Respiratory depression. Rapid recovery may cause possible "emergence delirium." Less biotransformation than other inhalation agents. Pungent smell may cause breath-holding during mask or chamber induction. Good muscle relaxation and analgesia; nonexplosive.

Nitrous oxide - potent analgesic; useful in conjunction with halothane and methoxyflurane; nonirritating; very insoluble in blood and tissues resulting in rapid induction and recovery; nonexplosive.

Diethyl ether - highly volatile and soluble; provides good analgesia and muscle relaxation; vapors irritate respiratory mucosa; VERY DANGEROUS as is flammable and highly explosive; not generally approved for use as an anesthetic agent at the NIH.

Chloroform - hepatotoxic and nephrotoxic in certain rodents; suspected human carcinogen; not generally approved for use as an anesthetic agent at the NIH.

Dissociative Agents (Ketamine, Tiletamine)

Dissociative anesthetics produce a state of chemical restraint and anesthesia characterized by a form of muscle rigidity and an apparent dissociation of the mind from the external environment (catalepsy) ; agents do not depress the central nervous system; reflexes remain intact; tracheal intubation possible; produce excessive salivation that is controllable with atropine.

These agents are do not have strong analgesic properties so their use must be limited to minor surgery or other procedures that are not likely to cause deep levels of pain. They can also be used in conjunction with other agents to provide greater analgesia.

Larger doses may produce convulsions.

Many adverse effects can be minimized by the addition of tranquilizers, like the benzodiazepines.

Example:

Ketamine hydrochloride (Vetalar® or Ketaset®) - preferred dissociative anesthetic due to a wide margin of safety; short duration and recovery time with few adverse side effects; poor muscle relaxation; contraindicated for use in animal with renal or hepatic disease.

Hypnotics (Propofol, Tribromoethanol)

Sedative hypnotics are nonselective CNS depressants producing a dose-dependent response ranging from sedation to surgical anesthesia, coma and death from depression of the respiratory and cardiovascular control centers.

Propofol is an alkylphenol, distinct from the barbiturates and imidazoles. The anesthetic properties of propofol are similar to thiopental, although recovery from a single dose of propofol is more rapid. Apnea occurs commonly in mice, rabbits, cats, and pigs, especially at higher doses. Propofol is generally considered a poor analgesic. Hypotension is a physiologic change which should be considered in animals with a compromised cardiovascular system.

Tribromoethanol produces a generalized CNS depression of both respiratory and cardiovascular centers. Intraperitoneal use in mice and small rodents results in rapid induction of short-term surgical anesthesia. Complications such as fibrinous peritonitis, intestinal ileus and impaired fertility may result if decomposition products (hydrobromic acid and dibromoacetaldehyde) develop due to improper preparation and storage. A 1.2% weight/volume solution should be prepared and storage at 4○C under dark conditions is crucial to avoid decomposition and subsequent mortality.

6.10 Analgesics:

Definition: Substances that temporarily alleviate pain without loss of consciousness.

Functional Uses:

Control pain without the use of anesthetics.

As a preanesthetic, it may reduce the amount of anesthetic that is required.

Relieve postoperative pain.

Narcotics (Opiates and Opioids):

Narcotic agents and narcotic antagonists all must be handled in adherence to the Controlled Substances Act.

Narcotics produce their major effects on the central nervous system (CNS) and bowel. Agents produce hypnotic and analgesic effects with resultant depression of the cardiovascular and thermoregulatory systems; attach to opiate sites in the CNS and block neurotransmitters, elevating the pain threshold.

Effects include analgesia, respiratory depression, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous systems.

Narcotics decrease the amount of other agents needed for general anesthesia by 1/3 to 1/2; most are metabolized by the liver and excreted in the bile and urine.

Actions and doses vary significantly among species. The actions of some analgesics have not been determined for some laboratory animals.

Morphine - used primarily in dogs and primates; can cause excitement in cats, horses, and food animals; duration of action of 4-6 hours; stimulates vomiting and vagal CNS centers; causes increased intraocular and intracranial pressure; relatively inexpensive.

Meperidine (Demerol®) - 1/10 as potent as morphine; preferred over morphine because of fewer side effects; used in dogs, cats, rodents, and primates; duration of action of 2-3 hours.

Fentanyl - potent, short acting, reversible narcotic used in Innovar-Vet; 100 times more potent than morphine; effects last 30-60 minutes.

Sufentanil (Sufenta®) - 200 to 250 times more potent than morphine.

Etorphine hydrochloride (M99) - synthetic derivative of the opium alkaloids; approximately 1000 times more potent than morphine; used for reversible immobilization of zoo animals and wild game.

Butorphanol (Torbugesic®) - Three to five times as potent as morphine.

Buprenorphine - A partial μ-agonist that produces analgesia and CNS side effects similar to morphine. It is 25 times as potent as morphine when given intramuscularly. It has a long duration of action. It has been shown to cause pica in rats.

Narcotic antagonists (e.g., naloxone, nalorphine) can prevent or promptly reverse the analgesic, gastrointestinal, depressant, and convulsant effects of opioids by displacing another compound at the receptor site; will not reverse the sedative or depressant effects of other drugs. Narcotic antagonists are Schedule III drugs.

Non-narcotic analgesics:

Xylazine (Rompun®) - a thiazine derivative which causes sedation, muscle relaxation, and analgesia; wide margin of safety; may cause emesis via direct central stimulation; potentiates barbiturate anesthesia; may precipitate early parturition if given to animals in last month of pregnancy; yohimbine or atipamezole reverse the effects of xylazine.

Non steroidal anti-inflammatory drugs (NSAIDS)- analgesic, antipyretic, and anti-inflammatory effects; aspirin is the best known; most effective for the relief of muscular pain and has minimal effect for the relief of visceral pain.

6.11 Neuromuscular Blocking Agents (Immobilizing Drugs or Paralytics):

Definition: Neuromuscular blocking agents inhibit the transmission of nerve impulses at the neuromuscular junction (e.g., succinylcholine) or at spinal synapses (e.g., mephenesin, guaifenesin) resulting in skeletal muscle paralysis and profound muscular relaxation without loss of consciousness.

Functional Use: Adjuvant in surgical anesthesia to obtain more complete muscle relaxation for procedures such as bone fracture repair in heavily muscled animals.

Effects:

Spinal polysynaptic reflexes are depressed preferentially over monosynaptic reflexes. Depolarizing neuromuscular blocking drugs (e.g., succinylcholine) interact with and depolarize the receptor areas, causing a lack of responsiveness to acetylcholine. These agents can not be reversed.Competitive neuromuscular blocking agents (e.g., d-tubocurarine, pancuronium) combine with the receptors and render them inaccessible to acetylcholine. These agents can be reversed. These agents produce muscle paralysis only, and do not produce either sedation or analgesia. These agents should never be used as anesthetic or analgesic agents (9 CFR 2.31; NRC, 1996; PHS, 1985).

Classification:

Depolarizing agents - decamethonium (Syncurine®) and succinylcholine (Anectine®).

Nondepolarizing agents - tubocurarine USP, gallamine (Flaxadil®), and pancuronium (Pavulon®).

REFERENCES

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